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Frequent *IDH2* R172 Mutations in Undifferentiated and Poorly-Differentiated Sinonasal Carcinomas

Snjezana Dogan[1,*], **Deborah J. Chute**[2], **Bin Xu**[3], **Ryan N. Ptashkin**[1], **Raghu Chandramohan**[1], **Jacklyn Casanova-Murphy**[1], **Khedoudja Nafa**[1], **Justin A. Bishop**[4], **Simion I. Chiosea**[5], **Edward B. Stelow**[6], **Ian Ganly**[7], **David G. Pfister**[8], **Nora Katabi**[1], **Ronald A. Ghossein**[1], and **Michael F. Berger**[1,9]

[1]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY

[2]Department of Pathology, Cleveland Clinic, Cleveland, OH

[3]Department of Pathology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

[4]Department of Pathology, The Johns Hopkins Hospital, Baltimore, MD

[5]Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA

[6]Department of Pathology, University of Virginia Health System, Charlottesville, VA

[7]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

[8]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

[9]Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Sinonasal undifferentiated carcinoma (SNUC) is a high-grade malignancy with limited treatment options and poor outcome. A morphologic spectrum of 47 sinonasal tumors including 17 (36.2%) SNUCs were analyzed at genomic level. Thirty carcinomas (Cohort 1) were subjected to a hybridization exon-capture next-generation sequencing assay (MSK-IMPACT™) to interrogate somatic variants in 279 or 410 cancer-related genes. Seventeen sinonasal tumors (Cohort 2) were examined only for presence of *IDH1/2* exon 4 mutations by Sanger sequencing. *IDH2* R172 single nucleotide variants were overall detected in 14 (82.4%) SNUCs, in 2 (20%) poorly-differentiated carcinomas with glandular/acinar differentiation, and in one of 2 high-grade neuroendocrine carcinomas, large cell type (HGNEC). No *IDH2* mutation was detected in any of 5 olfactory neuroblastomas or in any of 5 *SMARCB1*–deficient carcinomas.

Correspondence to: Snjezana Dogan MD, Department of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. dogans@mskcc.org.

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STATEMENT OF AUTHOR CONTRIBUTIONS

SD and MFB conceived the study, analyzed and interpreted the data. SD, DJC, NK, RAG, JAB, SIC, EBS provided samples. SD, NK, RAG and DJC performed histological review. RP performed FACETS analysis. BX performed statistical analysis. SD, DJC, BX, JAB, SIC, EBS, IG, DGP acquired the data. MFB, RC, KN and JC-M carried out experiments and analyzed the data. SD, MFB and RAG supervised the study. All authors were involved in writing the paper and had final approval of the manuscript.

Among 12 *IDH2*-mutated cases in Cohort 1, 5 (41.7%) harbored co-existing *TP53* mutations, 4 (33.3%) *CDKN2A/2B* loss-of-function alterations, 4 (33.3%) *MYC* amplification, and 3 (25%) had concurrent *SETD2* mutations. *AKT1* E17K and *KIT* D816V hotspot variants were each detected in one *IDH2*-mutated SNUC. The vast majority of SNUCs and variable proportions of other poorly differentiated sinonasal carcinomas may be amenable to IDH2-targeted therapy.

Keywords

IDH2 R172; SNUC; sinonasal undifferentiated carcinoma

INTRODUCTION

Sinonasal undifferentiated carcinoma (SNUC) is a rare aggressive malignancy of the sinonasal tract first described by Frierson *et al.* in 1986. SNUC patients typically present with large, locally invasive lesions that often destruct the orbital and/or cranial bones [1]. A multimodal therapy including chemoradiation and surgery offer the best treatment results. However, the outcome remains poor with the overall 5-year survival ranging between 22% and 42% [2,3]. Here, we performed a comprehensive genomic profiling of a cohort of SNUCs and a morphologic spectrum of high-grade/poorly-differentiated sinonasal carcinomas aiming (1) to identify potential novel molecular therapeutic targets, and (2) to explore the genetic differences between SNUC and other high-grade/poorly-differentiated sinonasal carcinomas in order to elucidate the pathogenesis of these tumors.

MATERIALS AND METHODS

Cases

Upon obtaining the Institutional Review Board (IRB) approval the pathology files of Memorial Sloan Kettering Cancer Center (MSKCC) were searched for sinonasal carcinomas diagnosed from January 1996 to January 2014 using the following criteria: (1) sinonasal undifferentiated carcinoma and (2) non-salivary and non-squamous high-grade/poorly-differentiated carcinomas with or without neuroendocrine or glandular differentiation. Twenty-two cases were retrieved. Six additional cases prospectively sequenced as clinical samples between January 2014 and February 2017 were added to the study. An additional 19 cases were received from three collaborating institutions after obtaining their respective IRBs approvals. Details on pathology slides review and ancillary studies results are provided in Supplementary material, Supplementary materials and methods, and supplementary material, [DOGAN comment: “Supplementary material” is repeated 2×. Also, I am not sure if it should be capitalized or not – here it is, below in the text is not (?)] Table S1. Cohort 1 (N=30, including matched metastasis in 2 cases) was profiled by MSK-IMPACT™ (MSK-Integrated Mutation Profiling of Actionable Cancer Targets). Cohort 2 (N=17) was examined for presence of *IDH1/2* exon 4 mutations by Sanger sequencing. The diagnostic spectrum of studied tumor categories is shown in Figure 1.

Immunohistochemistry and chromogenic *in situ* hybridization (CISH)

Immunohistochemistry and CISH were performed according to the manufacturer's recommendations (Ventana medical systems, Tucson, AZ), (supplementary material, supplementary materials and methods) using antibodies and CISH probes listed in supplementary material, Table S2.

DNA extraction and hybridization exon-capture next-generation sequencing

Tumors were profiled for genomic alterations in 279 or 410 key cancer-associated genes in 13 and 17 cases respectively, using our clinically validated custom deep sequencing MSK-IMPACT™ assay [4]. Twenty samples with matched normal DNA were selected for allele-specific copy number and cancer cell fraction (CCF) analysis by FACETS [5] rendering successful results in 19 samples (supplementary material, supplementary materials and methods).

Sanger DNA sequencing of IDH1 and IDH2

Sanger DNA sequencing of *IDH1/2* exon 4 was performed on ABI 3730 DNA sequencer (supplementary material, supplementary materials and methods) using primers listed in supplementary material, Table S3.

Statistical analysis

Statistical analyses were performed using SPSS software 22.0 (IBM Corporation, New York, NY). P values less than 0.05 were considered significant.

RESULTS AND DISCUSSION

Clinical features

Sinonasal carcinomas occurred in 29 men (61.7%) who were significantly younger than women presenting at the median age of 50 (range 33–95 years) and 72 (range 33–83 years), respectively (P=0.0006, two-tailed Student's t-Test); (supplementary material, Table S1). Most (83.3%) cases were detected as multi-compartmental masses rendering the majority (86.7%) of patients to present at clinical stage IV. Multimodal treatment was administered in 83.3% cases and included surgery with radiation and/or chemotherapy (Table 1).

Genomic profile by MSK-IMPACT™

Most notably, *IDH2* R172 mutations were detected in 12 (40%) carcinomas of various histologic types, and *SMARCB1* deletions were detected in 4 (13.3%) cases. Frequent alterations involved tumor suppressor genes including *TP53* (33.3%), *CDKN2A/CDKN2B* (16.7%), *RB1* (10%) and *TSC1* (10%). Loss of heterozygosity (LOH) was detected in 4 of 5 *TP53*-mutated cases, and in 2 of 3 *TSC1*-mutated carcinomas (Figure 2A). Aside from *IDH2* and *SMARCB1,* recurrent alterations were detected in other epigenetically important genes including *CREBBP* (13.3%), and *SETD2* (10%), and in the oncogenes *MYC* (16.7%) and *KRAS* (10%), including *KRAS* G12D variant in one SNUC; (Figure 2A). Copy number analysis revealed frequent gains involving chromosomes 8 and 20, and chromosome arms 1q

and 17q; recurrent losses were detected in 3p, and in chromosomes 13, 14, 15, 16, and 18. Notably, the majority of SNUCs showed 8q gain (71.4%), and 3p loss (57.1%); (Figure 2B).

a. IDH2-mutated sinonasal carcinomas—Activating hotspot *IDH1/IDH2* mutations have been identified in various cancers. *IDH1* mutations are predominant in solid tumors; gliomas [6], chondrosarcomas [7], and intrahepatic cholangiocarcinoma [8]. *IDH2* mutations are more frequent in acute myeloid leukemia (AML) [9] and angioimmunoblastic T-cell lymphoma [10]. IDH1 (isocitrate dehydrogenase 1) and IDH2 (isocitrate dehydrogenase 2) are homodimeric enzymes that catalyze the conversion of isocitrate to α-ketoglutarate. The mutant protein, IDH1 or IDH2, loses its normal enzymatic activity and acquires a gain-of-function neomorphic enzymatic activity leading to abnormally increased levels of "oncometabolite" (R)-2-hydroxyglutarate [9]. In all except one low tumor purity sample, the CCF with *IDH2* R172 mutation was high (average 0.87, range 0.4–1.0) (supplementary material, Table S4). In the case with matched metastasis, the CCF indicated the presence of *IDH2* variant in (nearly) all cancer cells at both sites suggesting they are likely clonal (Figure 3). Among 12 *IDH2*-mutated cases, co-existing recurrent alterations were detected in *TP53* (41.7%), *CDKN2A/2B* (33.3%), *MYC* (33.3%), *SETD2* (25%), and *SPEN* (16.7%).

Three (25%) cases harbored a second, non-hotspot *IDH2* mutation. *AKT1* E17K and *KIT* D816V hotspot variants were each detected in one case. *IDH1/2* pathogenic mutations were often found to co-exist with mutations affecting other oncogenic pathways. Studies on *IDH1/2*-mutated gliomas give a notion that the glial cells may become susceptible to mutant *IDH1* through activation of MAPK, PI3K/Akt, and MYC, and loss of p53 signaling [11]. We hypothesize that the concurrent genetic alterations in *IDH2*-mutated sinonasal carcinomas may collaborate with mutant *IDH2* to induce and promote carcinogenesis in these tumors.

High frequency of *IDH2* mutations in Cohort 1 prompted a testing of an extended set of sinonasal tumors for presence of *IDH1/2* hotspot mutations by Sanger sequencing (Cohort 2, N=17). The frequencies and distribution of *IDH2* mutations in both Cohorts (N=47) are provided in Figure 1. *IDH2* R172S (58.8%), R172T (23.5%), R172M (11.8%) and R172G (5.9%) were found in 12 (70.6%) men (median age 49, range 39–85 years), and 5 (29.4%) women (median age 62, range 49–83 years); (supplementary material, Table S1). In a recent study of 11 SNUCs, Jo *et al.* found *IDH2* R172 mutations in 55% cases [12]. In addition to the higher *IDH2* mutation detection rate in SNUC, the results of our larger, histologically diverse cohort show that (1) *IDH2* mutations can also be found in poorly-differentiated sinonasal carcinomas other than SNUC, (2) they are likely clonal (in most cases), and (3) frequently co-exist with *MYC* amplifications.

Clinical trials with established targeted therapies against IDH2 mutant proteins are in progress. Preliminary findings of an ongoing phase 1 clinical trial have shown that the mutant IDH2-inhibitor AG-221 produces clinical responses in about 40% of patients with AML and myelodysplastic syndrome [13]. These results may provide rationale for taking a similar approach in treatment of *IDH2*-mutated sinonasal carcinomas.

Morphologically, except for one poorly-differentiated non-intestinal type adenocarcinoma, all *IDH2*-mutated tumors were arranged in sheets or lobules. Irrespective of the final

diagnosis, they shared very similar cytological features and consisted of large undifferentiated epithelial tumor cells in most cases (Figure 3, supplementary material, Figure S1). However, they were not notably morphologically distinct from their *IDH2*-wild type histological counterparts (supplementary material, Figure S2). Functional studies on different cell lines including murine bone marrow cells, adipocytes, and astrocytes showed that increased intracellular (R)-2-hydroxyglutarate lead to hypermethylation of target genes and the subsequent block in cellular differentiation [14–16]. *IDH2* mutations in sinonasal carcinomas may have similar consequences leading to block in cellular differentiation and resulting in either undifferentiated or poorly-differentiated carcinomas in this location.

The outcome in respect to the *IDH2* mutation status is provided in Table 1. Although *IDH2*-mutated sinonasal carcinomas were associated with a trend of improved disease free survival and overall survival, such trend did not reach significant level (log rank test, P=0.112 and P=0.145, respectively); (supplementary material, Figure S3).

b. SMARCB1-deficient sinonasal carcinomas—*SMARCB1* deletions detected in Cohort 1 occurred in 4 men (age range 47–95 years); (Table 1). *SMARCB1*-deficient sinonasal carcinomas displayed a relative paucity of co-existing mutations emphasizing the oncogenic role of *SMARCB1* loss in these tumors (Figure 2, supplementary material, Table S5).

c. Small cell neuroendocrine carcinoma (SCNEC) of the sinonasal tract—In one SCNEC, *ERBB3* V104L co-existed with *TP53* mutations, and *BCL2* and *MYC* amplifications. In another, along with *TP53* and *CREBBP* mutations, there were two pathogenic *RB1* mutations and one likely loss-of-function *INPP4B* mutation (Figure 2, supplementary material, Figure S4). Mutations of *TP53* and *RB1*, up-regulation of *BCL2* signaling, and activation of *MYC* and PI3K pathways are frequent in pulmonary small cell carcinomas [17]. A notable similarity in the mutational profiles of sinonasal SCNEC and its lung counterpart supports their common genetic background. Novel findings, *ERBB3* V104L oncogenic mutation [18] and *INPP4B* loss-of-function mutation may represent alternate mechanisms of PI3K/Akt pathway activation [19] in sinonasal SCNECs.

In conclusion, given the established knowledge on the biological significance of *IDH1/2* mutations in other cancer types, our results suggest the *IDH2* R172 mutations may play an important role in carcinogenesis of SNUC. *IDH2*-mutated sinonasal carcinomas may be amenable to IDH2-targeted therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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	Tumor type	Sequencing method			*IDH1/IDH2* mutation status	
		MSK-IMPACT™ (Cohort 1, N=30)	Sanger for exon 4 *IDH1/IDH2* (Cohort 2, N=17)	Total cases (N=47)	*IDH1*-mutated (%)	*IDH2*-mutated (%)
1	Sinonasal undifferentiated carcinoma	10	7	17	0	14 (82.4%)
2	Poorly-differentiated non-intestinal type adenocarcinoma / Poorly-differentiated carcinoma with focal glandular/acinar differentiation	9	1	10	0	2 (20%)
3	High-grade neuroendocrine carcinoma, large cell type	1	1	2	0	1 (50%)
4	*SMARCB1*-deficient sinonasal carcinoma	4	1	5	0	0
5	Small cell neuroendocrine carcinoma	2	0	2	0	0
6	Moderately-differentiated intestinal type adenocarcinoma	2	1	3	0	0
7	Poorly-differentiated carcinoma with neuroendocrine and glandular differentiation	1	1	2	0	0
8	NUT midline carcinoma	1	0	1	0	0
9	Olfactory neuroblastoma	0	5	5	0	0

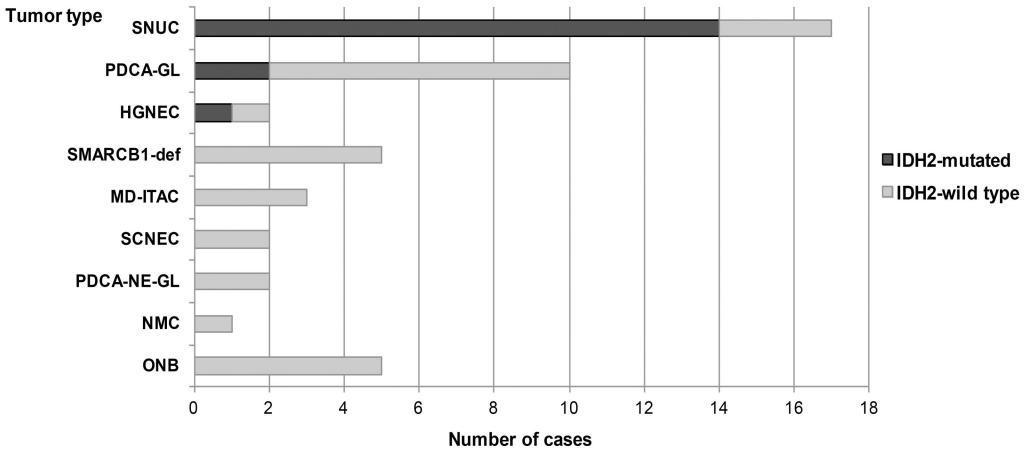

Figure 1. Frequencies of *IDH1* and *IDH2* mutations in sinonasal carcinomas and olfactory neuroblastoma

Abbreviations: SNUC=sinonasal undifferentiated carcinoma, PDCA-GL=poorly differentiated non-intestinal type adenocarcinoma/poorly-differentiated carcinoma with focal glandular differentiation, HGNEC=high-grade neuroendocrine carcinoma, large cell type, SCNEC=small cell neuroendocrine carcinoma, *SMARCB1*-def= *SMARCB1*-deficient sinonasal carcinoma, NMC=NUT midline carcinoma, MD-ITAC=moderately-differentiated intestinal type adenocarcinoma with signet-ring cells and mucinous features, PDCA-NE-GL=poorly differentiated carcinoma with neuroendocrine and glandular differentiation, ONB=olfactory neuroblastoma.

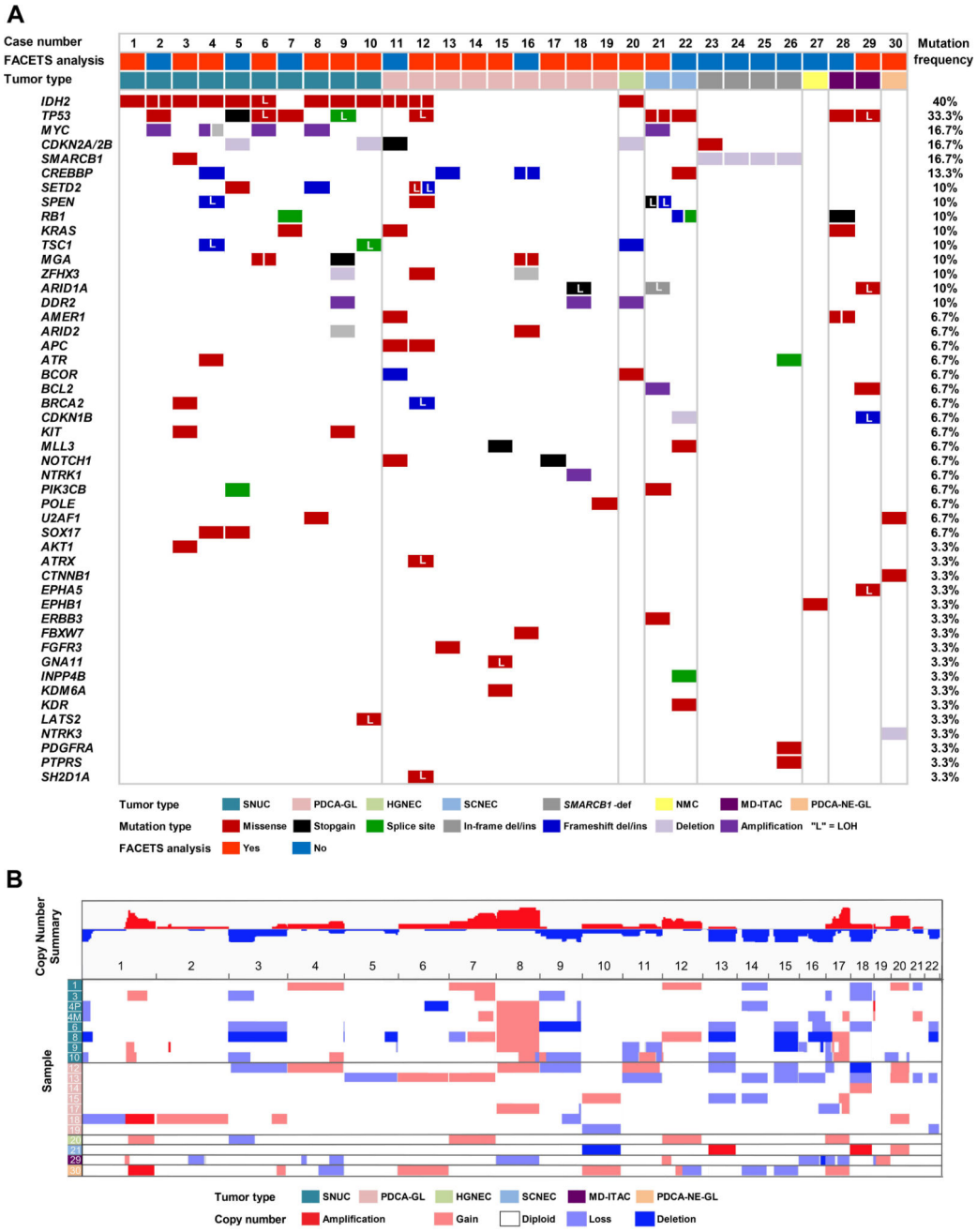

Figure 2.

Genetic alterations detected by MSK-IMPACT™ in sinonasal carcinomas (Cohort 1). A. Cases are represented in columns; genes are depicted in rows. Tumor types and mutation types are color-coded according to the legend. B. Spectrum of somatic copy number alterations identified in sinonasal carcinomas detected by FACETS [5]. Genome wide copy number alterations are color-coded according to the legend and summarized at the cohort level and by tumor type.

Abbreviations: SNUC=sinonasal undifferentiated carcinoma, PDCA-GL=poorly differentiated non-intestinal type adenocarcinoma/poorly-differentiated carcinoma with focal

glandular/acinar differentiation, HGNEC=high-grade neuroendocrine carcinoma, large cell type, SCNEC=small cell neuroendocrine carcinoma, *SMARCB1*-def= *SMARCB1*-deficient sinonasal carcinoma, NMC=NUT midline carcinoma, MD-ITAC=moderately-differentiated intestinal type adenocarcinoma, PDCA-NE-GL=poorly differentiated carcinoma with neuroendocrine and glandular differentiation, LOH=loss of heterozygosity.

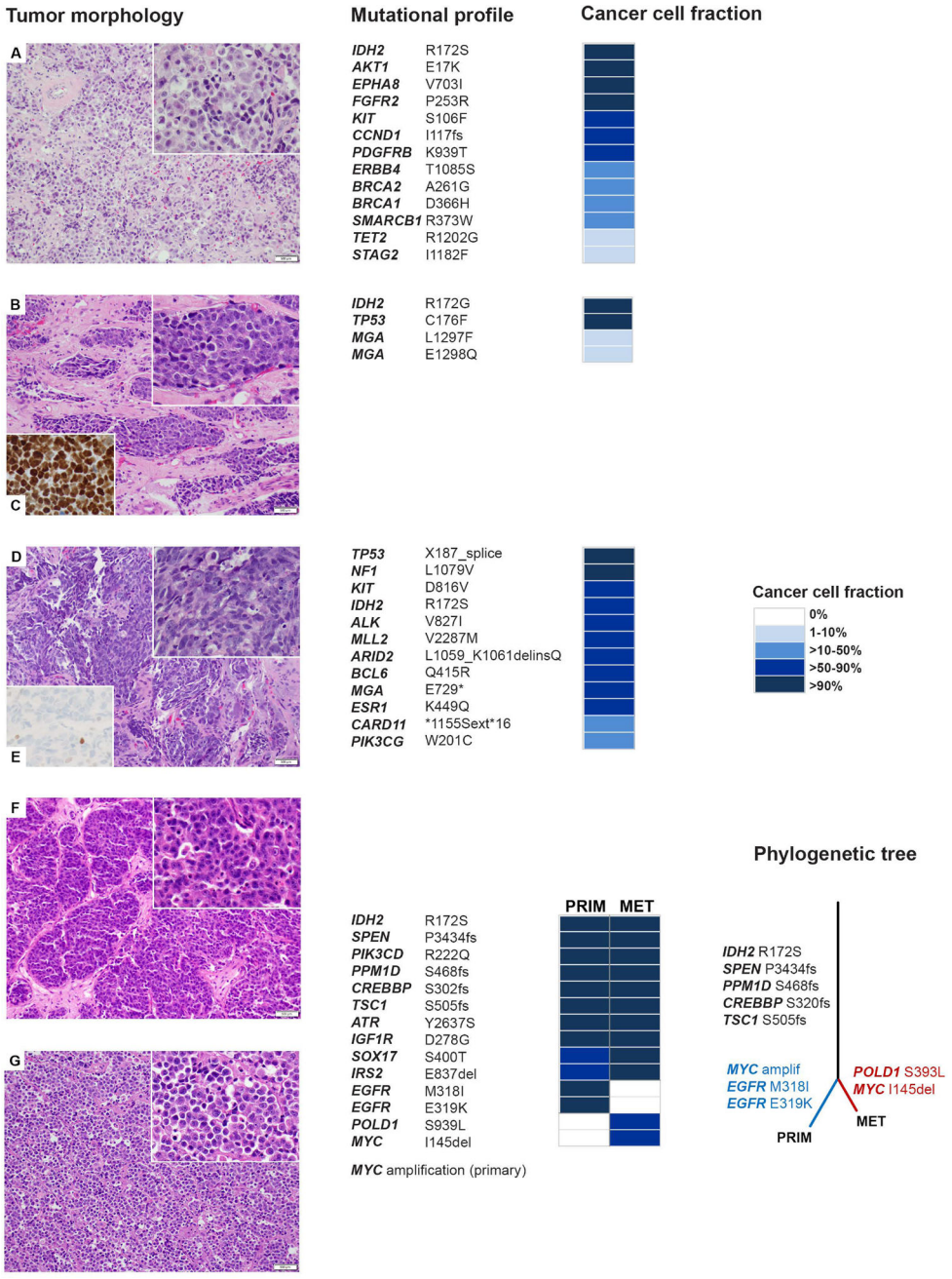

Figure 3.

Phenotype and genetics of *IDH2*-mutated SNUC. Histology of the *IDH2*-mutated SNUCs including the matched metastasis in case 4 (G, 200× magnification) are shown with their respective genome plots and mutational profiles. Large undifferentiated epithelial tumor cells display high nuclear/cytoplasmic ratio, and in most cases they show open chromatin and prominent cherry-red nucleoli (insets A, B, D, F and G, 400× magnification). In case 6, somatic mutation in *TP53* is consistent with an increased nuclear expression of p53 protein (C, 400× magnification), whereas in case 9, *TP53* splice site variant with loss of heterozygosity is compatible with an absence of p53 protein (E, 400× magnification). In

case 4, on the far right, the phylogenetic tree illustrates the clonal evolution of the primary tumor and the metastasis. The length of branches corresponds to the number of somatic mutations that distinguishes the primary or metastatic clone from their parental clone [22]. Key to cases: A=case 3, B, C=case 6, D, E=case 9, F=case 4, primary tumor, G=case 4, metastasis. Abbreviations: PRIM=primary tumor, MET= metastasis, amplif=amplification.

Table 1

Clinical presentation and the outcome of patients with sinonasal carcinomas (Cohort 1).

Case number	Sex	Age	Location	Symptoms at presentation	Diagnosis	*IDH2* status	Size (cm)	T stage	N stage	M stage	Clinical Stage	Primary treatment (post-recurrence treatment)	Recurrence	Disease status at last follow-up (months)
1	M	61	Ethmoid sinus	Memory loss, personality changes	SNUC	Mutated	NA	cT4a	cN0	cM0	IVA	SX+RTCT	No	NED (102)
2	M	57	Ethmoid sinus and nasal cavity	Eye pain, proptosis	SNUC	Mutated	5.1	cT4b	cN0	cM0	IVB	SX+RTCX	Local recurrence and distant metastasis (bone, liver, abdominal lymph nodes)	DOD (6)
3	F	49	Ethmoid sinus and nasal cavity	Nasal congestion, headache	SNUC	Mutated	NA	cT4a	cN0	cM0	IVA	SX+RT	Regional metastasis (lymph nodes) and distant metastasis (liver)	AWD (13)
4	M	48	Nasal cavity	Double vision, swelling and proptosis of the eye, nasal obstruction	SNUC	Mutated	6.2	pT4b	cN2a	cM0	IVB	SX+RTCX	Distant metastasis (bone) and regional metastasis (skin)	DOD (18)
5	M	43	Ethmoid sinus and nasal cavity	Nasal congestion, loss of smell and taste, supra-orbital headaches	SNUC	Mutated	7	cT4b	cN2c	cM0	IVB	RTCX	No	NED (40)
6	M	49	Ethmoid sinus and nasal cavity	Nasal congestion, decrease in taste and smell	SNUC	Mutated	5	pT3	cN0	cM0	III	SX+RTCX	No	NED (103)
7	F	74	Sphenoid sinus	Nasal congestion, epistaxis, headache	SNUC	wt	3	cT4a	cN0	cM0	IVA	NRTCX+SX	No	NED (96)
8	F	72	Nasal cavity	Visual changes, orbital pressure sensation	SNUC	Mutated	4.5	cT4b	cN0	cM0	IVB	RTCX	No	AWD (30)
9	M	53	Ethmoid sinus and nasal cavity	Nasal congestion	SNUC *in situ*	Mutated	N/A	pTis	cN0	cM0	0	SX (RTCX)	Local recurrence (soft palate)	NED (70)
10	M	44	Nasal cavity	Facial pain, swelling	SNUC	Mutated	5.2	cT4b	cN2	cM0	IVB	CX	Distant metastasis (adrenal gland)	DOD (15)
11	F	83	Ethmoid sinus and nasal cavity	Nasal obstruction, epistaxis	PD non-ITAC	Mutated	2.5	cT2	cN0	cM0	II	SX+RT	No	DOUC (69)
12	M	39	Nasal cavity	Nasal obstruction	PDCA with focal glandular/acinar differentiation	Mutated	5	pT4a	cN0	cM0	IVA	NCX+SX+RTCX	Regional metastasis (lymph nodes) and local recurrence	DOD (33)
13	F	65	Nasal septum	Nasal obstruction	PDCA with focal glandular/acinar differentiation	wt	2.8	cT2	cN0	cM0	II	SX+RT (RTCX for local recurrence)	Local recurrence, distant metastasis (bone)	DOD (34)
14	M	49	Maxillary sinus	Headaches, ear obstruction, maxillary and facial pain, diplopia, eye swelling	PDCA with focal glandular/acinar differentiation	wt	NA	cT4b	cN0	cM0	IVB	RTCX	No	AWD (14)

Case number	Sex	Age	Location	Symptoms at presentation	Diagnosis	*IDH2* status	Size (cm)	T stage	N stage	M stage	Clinical Stage	Primary treatment (post-recurrence treatment)	Recurrence	Disease status at last follow-up (months)
15	M	47	Ethmoid sinus	Headaches, blurred vision, facial pain, ear pain, eye swelling	PDCA with focal glandular/acinar differentiation	wt	4.4	cT4b	cN0	cM0	IVB	SX+RTCX	Local recurrence and distant metastasis (bone, liver, abdominal lymph nodes)	DOD (24)
16	M	56	Nasal cavity	Headache, weakness, poor appetite	PDCA with focal glandular/acinar differentiation	wt	4.6	cT4b	cN0	cM1	IVC	RTCX	Local recurrence and distant metastasis (liver)	DOD (16)
17	M	51	Sphenoid sinus	Headache, nasal congestion	PDCA with focal glandular/acinar differentiation	wt	4.5	pT4a	cN0	cM0	IVA	SX+RTCX	Local recurrence and distant metastasis (bone)	DOD (28)
18	M	44	Ethmoid sinus and nasal cavity	Nasal congestion, epistaxis	Non-ITAC, HG	wt	6.5	cT4a	cN0	cM0	IVA	SX+RTCX	No	NED (10)
19	F	30	Nasal cavity	Nasal congestion, visual changes, sensation deficits	PDCA with focal glandular/acinar differentiation	wt	4.8	pT4b	cN0	cM0	IVB	NCX+SX+RTCX (RT)	Local recurrence (orbit) and distant metastasis (spine, pleura, adrenal gland)	DOD (30)
20	M	45	Ethmoid sinus	Headache	HGNEC	Mutated	3.1	cT4a	pN2b	cM0	IVA	SX (RTCX for local recurrence)	Local recurrence	NED (60)
21	F	62	Ethmoid sinus and nasal cavity	Sinus congestion, facial pain, occasional double vision	SCNEC	wt	4.6	cT4b	cN0	cM1	IVC	CX+RT	Local recurrence and distant metastasis (bone)	DOD (7)
22	F	62	Ethmoid sinus and nasal cavity	Nasal congestion, epistaxis	SCNEC	wt	3.4	pT4b	cN0	cM0	IVB	SX+RTCX	Local recurrence and distant metastasis (lung)	AWD (21)
23	M	54	Ethmoid sinus and nasal cavity	Nasal congestion	*SMARCB1*-deficient sinonasal carcinoma	wt	2.6	cT4a	cN0	cM0	IVA	SX (RTCX for local recurrence)	Distant metastasis (bone, brain)	DOD (39)
24	M	47	Ethmoid sinus	Nasal congestion, epistaxis, pain above eye	*SMARCB1*-deficient sinonasal carcinoma	wt	4.0	cT4b	cN0	cM0	IVB	NRTCX+SX	Local recurrence	AWD (7)
25	M	54	Ethmoid sinus and nasal cavity	Epistaxis	*SMARCB1*-deficient sinonasal carcinoma	wt	4.5	cT4b	cN0	cM0	IVB	NCX + SX	Local recurrence and distant metastasis (bone)	AWD (23)
26	M	95	Ethmoid sinus and nasal cavity	Progressive mental and gait deficit, behavioral changes	*SMARCB1*-deficient sinonasal carcinoma	wt	NA	cT4b	cN0	cM0	IVB	SX	N/A	N/A
27	F	77	Ethmoid sinus	Nasal congestion, obstruction, and purulent drainage	NUT midline carcinoma	wt	NA	cT4b	cN0	cM0	IVB	RT	Local recurrence and distant metastasis (bone, lung, mediastinum)	DOD (5)
28	F	76	Nasal cavity	Nasal congestion	MD-ITAC with signet-ring cells and mucinous features	wt	NA	cT4a	cN0	cM0	IVA	SX+RT	Local recurrence and regional metastasis (lymph nodes)	DOD (24)
29	M	80	Clivus/skull base	Visual changes, rhinorrhea	MD-ITAC	wt	5.0	cT4b	cN0	cM0	IVB	RTCX	No	AWD (7)

Case number	Sex	Age	Location	Symptoms at presentation	Diagnosis	*IDH2* status	Size (cm)	T stage	N stage	M stage	Clinical Stage	Primary treatment (post-recurrence treatment)	Recurrence	Disease status at last follow-up (months)
30	F	81	Nasal cavity	Epistaxis	PDCA with neuroendocrine and glandular differentiation	wt	5.9	cT4a	cN0	cM0	IVA	SX+RT	No	NED (37)

Abbreviations: SNUC=sinonasal undifferentiated carcinoma, HGCA=high-grade carcinoma, PDCA=poorly-differentiated carcinoma, HGNEC=high-grade neuroendocrine carcinoma, large cell type, MD-ITAC=moderately-differentiated intestinal type adenocarcinoma, SCNEC=small cell neuroendocrine carcinoma, HG=high-grade,wt=wild type, SX=surgery, RT=radiation therapy, RTCX=chemoradiation, NCX=neoadjuvant chemotherapy, NRTCX=neoadjuvant chemoradiation, DOD=died of disease, AWD=alive with disease, NED=no evidence of disease, DOUC=died of unknown causes.